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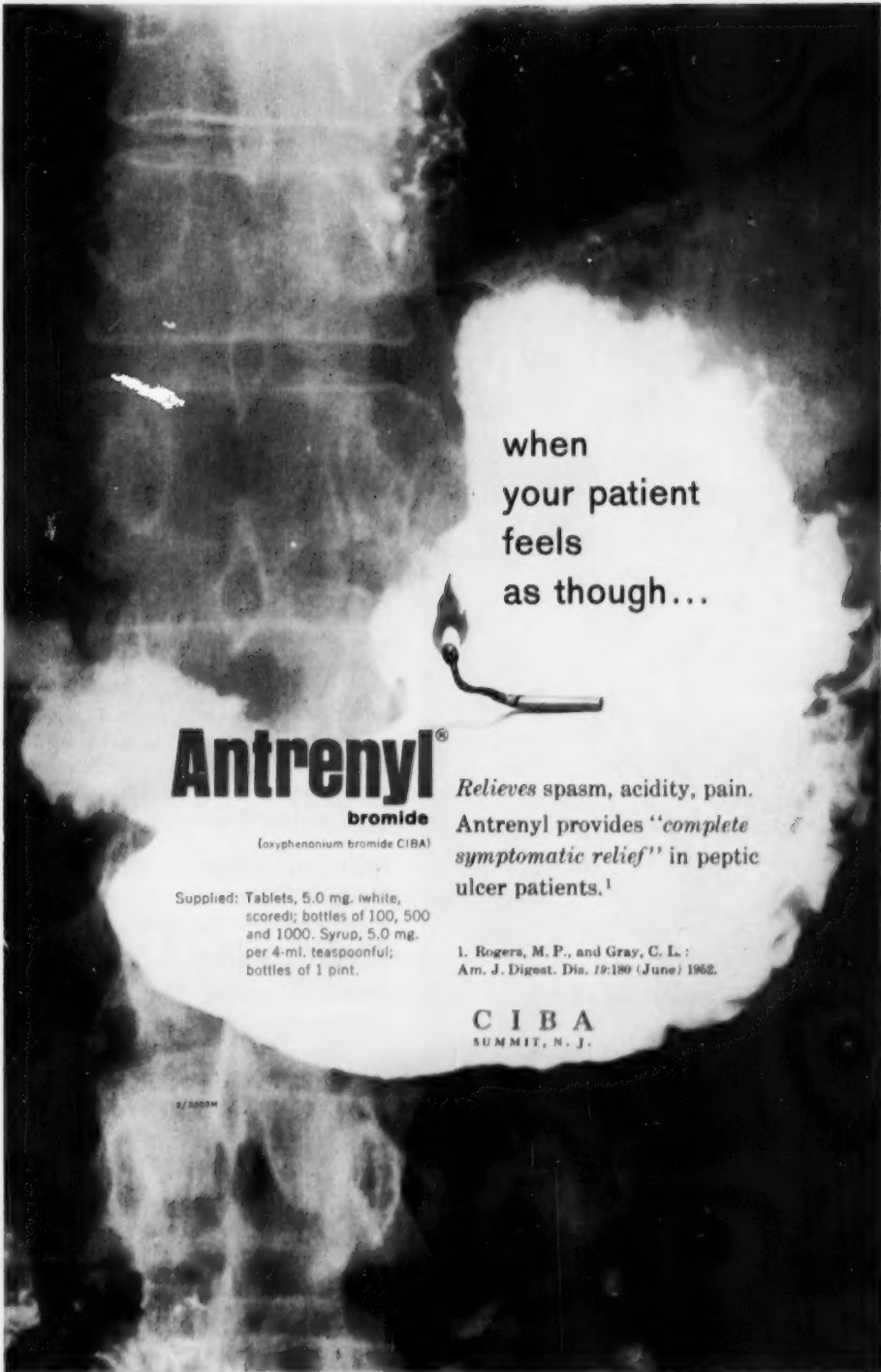
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1. Rogers, M. P., and Gray, C. L.:
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New Series Volume 1 Number 5

May 1956

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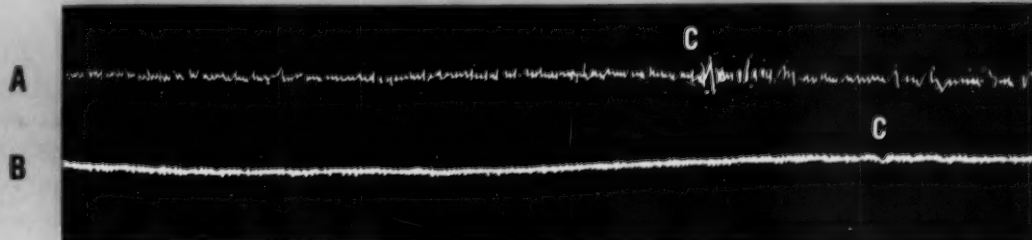
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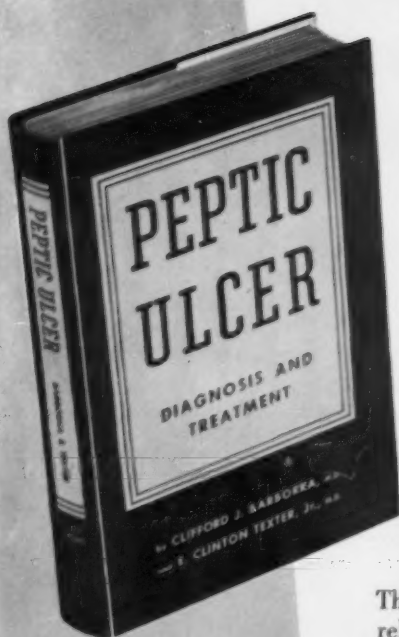
1. Dickel, H.A., et al.: *West. J. Surg.*, April, 1956.

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- Anticholinergic Drugs
- Other Therapeutic Adjuncts
- Complications and Their Management
- Surgical Treatment
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1. Recommended Dietary Allowances, Washington, D. C., National Academy of Sciences—National Research Council, Publication 302, 1953.
2. Co Tui: Review: The Fundamentals of Clinical Proteinology, *J. Clin. Nutrition* 7:232 (Mar.-Apr.) 1953.
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1. Weiss, S. et al. *Amer. J. Gastroenterol.* 24:523, Nov. 1955.

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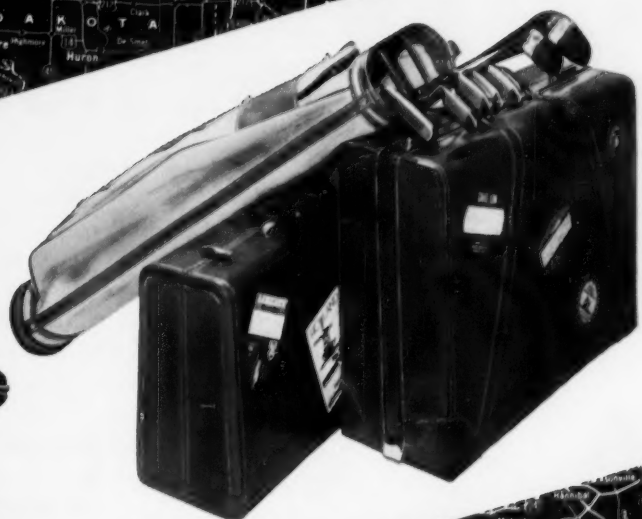
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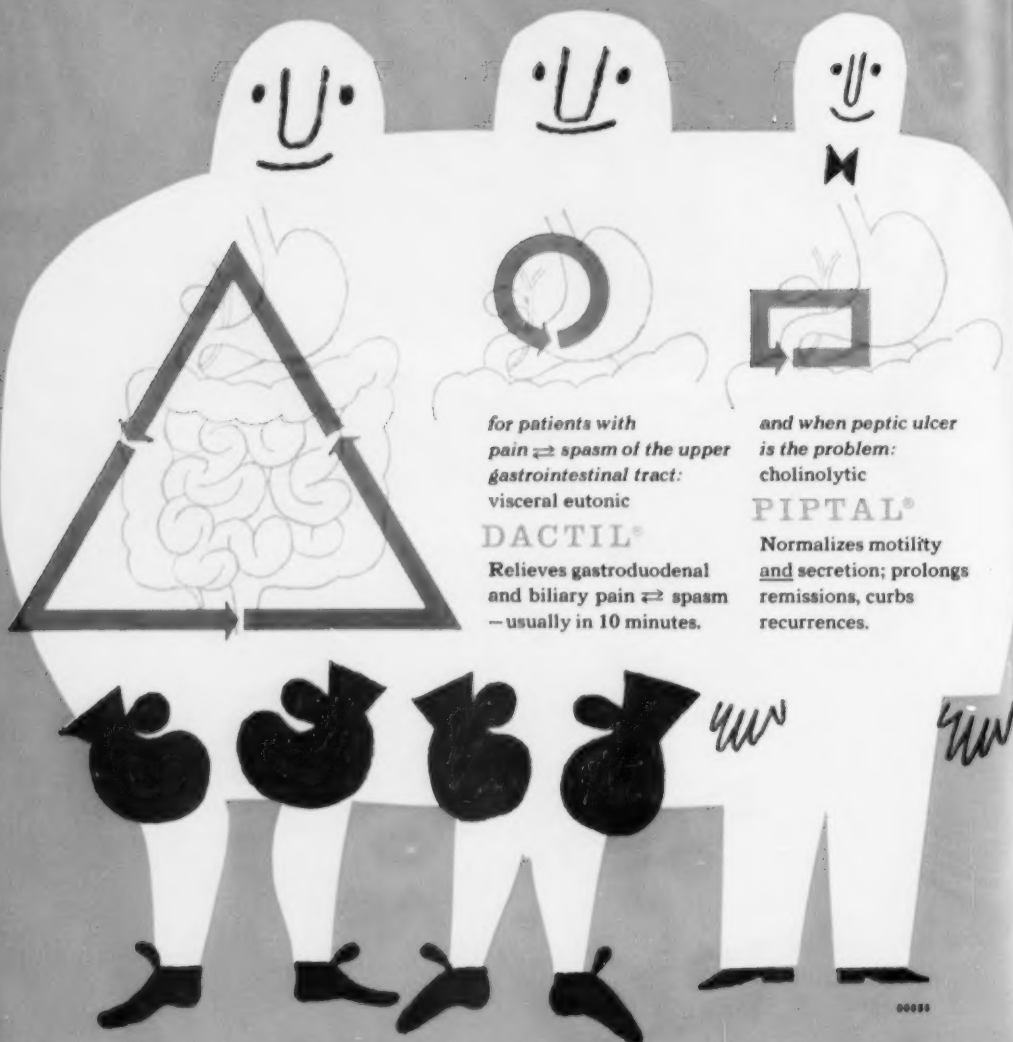


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L LAKESIDE

Hematemesis and Melena in Cambridge

A. P. WATERTON, M.D.

THE MORTALITY from serious gastric and upper intestinal hemorrhage varies with the underlying disease, with the age of the patients in the group studied, and with the methods of treatment. One or all of these factors may change significantly within a few years in one place, and all may vary from country to country, or within a country at one time. It is therefore necessary continually to review the causes of such bleeding, the history of the patients concerned, and the nature and results of the treatment they receive.

MATERIAL

Addenbrooke's Hospital is a large provincial hospital which is particularly suited for a study of this kind. It serves the city of Cambridge and a fairly well-defined area around it, and being the only general hospital in the neighborhood its patients include nearly all those in the area needing hospitalization. Thus the picture of any one disease is a truthful reflection of the actual state of affairs. The present study encompasses all patients admitted to the general wards because of hematemesis or melena during the 20-month period October, 1950, to June, 1952. During this time a few such cases were treated in private wards or nursing homes, but there is reason to believe that this number was very small. Inquiry of general practitioners suggests that the cases admitted to the hospital represent about one fifth of all the cases seen by doctors during the period, the majority being mild cases easily treated at home. Children under age 10 have been excluded.

CAUSES OF BLEEDING

There were 170 admissions for hematemesis and melena during the 20 months. These involved 165 patients, 5 admissions being for fresh hemorrhage in patients admitted earlier in the series. The diagnoses are shown in Table 1.

From the Department of Pathology, University of Cambridge, Cambridge, England.

I am indebted to the consultant staff of Addenbrooke's Hospital for access to their patients, and particularly to Dr. Laurence Martin for his stimulating interest in the subject of gastrointestinal bleeding.

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Waterson

TABLE 1. Causes of Bleeding in 170 Patients with Hematemesis and Melena

	No. cases
Proved or probable peptic ulcer	154
Other causes	16
Gastric tumors	
Benign (leiomyoma)	1
Malignant	0
Portal hypertension with esophageal varices (1 case of Banti's syndrome and 1 case of hepatic cirrhosis, admitted twice)	3
Esophageal hiatus hernia (1 with radiologically demonstrable small esophageal varices, 1 with a traction diverticulum of the lower esophagus)	3
Blood disorders	
Thrombocytopenic purpura	1
Chronic myeloid leukaemia	1
Meckel's diverticulum	1
Duodenal diverticulum	1
Erosion of aorta and duodenum by tuberculous lymph node	1
Carcinoma of pancreas	1
Cases considered to have been provoked by aspirin	3

The salient features of the table are that in 154 (90.6 per cent) of the 170 cases the cause of the bleeding was "proved or probable peptic ulcer," that there were very few admissions for bleeding from esophageal varices, and that during this period no patients with hemorrhage from gastric carcinoma were admitted. Esophageal hiatus hernia is probably a commoner cause than has until recently been realized. In nearly every case in the present series inquiry has been made specifically about the taking of aspirin and other salicylates. The results of this investigation are reported separately.⁷

BLEEDING PEPTIC ULCER

The cases of bleeding peptic ulcer may be grouped as shown in Table 2. The age and sex distribution according to type of ulcer is given in Table 3. More than three quarters (78.0 per cent) of the patients were aged 50 or over. Only a fifth (22.0 per cent) were women, and nearly half of all the cases (46.2 per cent) were cases of duodenal ulcer. Most of the small group of 12 incompletely investigated cases were elderly people in whom such factors as a comparatively mild hemorrhage or a complete lack of cooperation made further examination not worth while.

"X-ray-negative" Cases

The 34 cases in which opaque-meal radiography during convalescence failed to show evidence of a gastric or duodenal ulcer are classed as "X-ray-negative." Most of such patients have probably an acute

Hematemesis and Melena

TABLE 2. Proved or Probable Peptic Ulcer

	No. cases
Chronic gastric ulcer	32
Duodenal ulcer (including 5 cases after gastroenterostomy, and 1 case after partial gastrectomy, for duodenal ulcer)	71
Acute-lesion group (proved by operation or radiography)	5
Duodenitis (2 cases), acute gastric ulcer (1 case), gastric erosion (1 case), multiple acute erosions (1 case)	
"X-ray-negative" cases	34
Incompletely investigated cases	12
TOTAL	154

TABLE 3. Age and Sex Distribution of Patients According to Type of Peptic Ulcer

Age group	Chronic gastric ulcer		Duodenal ulcer		Acute-lesion group		Incomplete investigation		Totals	
	M	F	M	F	M	F	M	F	M	F
10-19	1	1	..
20-29	1	..	2	1	1	4	1
30-39	1	..	5	1	2	8	1
40-49	5	..	9	3	6	4	20	7
50-59	9	3	15	3	8	2	1	1	33	9
60-69	11	1	16	2	4	5	1	1	32	9
70-79	..	1	12	2	4	2	4	2	20	7
80-89	2	..	2	..
TOTALS	27	5	59	12	26	13	8	4	120	34

gastric ulcer, and may be distinguished from patients with chronic gastric ulcer by their equal distribution between the two sexes, by the fact that recent pain is usually of not more than 2 weeks' duration, and by their good prognosis.¹⁻⁶ Norbye also confirmed that X-ray-negative cases have a shorter dyspeptic history. These 34 cases in the present series differed from the 32 cases of proved chronic gastric ulcer in several ways:

1. Twelve of the 34 (35.3 per cent) were women as opposed to 5 out of 32 (15.6 per cent) in cases of chronic gastric ulcer.

2. The period of recent pain before hemorrhage was longer than 2 weeks in only 5 of the X-ray-negative group, compared to 21 of the chronic-ulcer patients.

3. None of these 34 X-ray-negative patients died, as opposed to the 6 deaths in 32 patients with chronic gastric ulcer.

Waterson

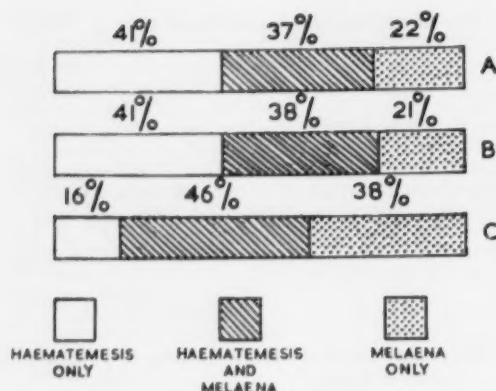


Fig. 1. The diagram represents the number of patients, expressed as a percentage, who gave a history of hematemesis only, hematemesis and melena, and melena only, in each of three diagnostic groups: A, chronic gastric ulcer; B, "X-ray-negative" group; C, duodenal ulcer.

4. Fractional test meals were done in only 8 of these 34 patients, with these results: hyperchlorhydria, 2; normal, 2; hypochlorhydria, 2; and prehistamine achlorhydria, 2.

5. The history of the X-ray-negative group hemorrhage was more like that of patients with a known gastric ulcer than like the duodenal-ulcer histories. Figure 1 is a graphic summary of history of hematemesis or melena or both before admission, for each of the three groups. The association of hematemesis with the X-ray-negative and melena with the known-duodenal-ulcer group, while not complete, is strong enough to suggest that the site of the bleeding in the former patients was in the stomach.

Mortality

Of the 154 patients, 16 died in the hospital, an over-all mortality rate of 10.4 per cent. One of these was a man who recovered from the hemorrhage and died 75 days after admission of a bronchial carcinoma, whose first manifestation was a pleural effusion during convalescence. Apart from this, no deaths have been excluded, and the corrected mortality rate is therefore 15 out of 154 (9.7 per cent). The details of the deaths are set out in Table 4. The factors influencing mortality will be considered with regard to the hemorrhage itself, the ulcer, and the patient.

Influence of Hemorrhage

The volume of blood transfused gives an approximate measure of the total blood lost during the time in hospital and immediately before admission.¹

Hematemesis and Melena

Amount of blood (cc.) given	No. patients	No. deaths
0	44	2
500-2500	83	6 (3 postoperative)
3000-5000	14	2
More than 5000	13	5 (2 postoperative)

The 2 patients who died without transfusion were a moribund man who died within half an hour of admission, and a woman of 73 with severe cardiac failure. The figure of 5 deaths in 13 patients who had more than 10 bottles is significantly higher than that of 10 in 141 who had 10 or less ($\chi^2 = 10.0$; $p = 0.001$, approx.).

Brisk recurrent hemorrhage in hospital, as manifested clinically by hematemesis, sudden collapse, or sudden melena, has previously been shown to be of serious prognostic significance (Table 5).

The mortality of the series as a whole is significantly higher in the group with brisk recurrent hemorrhage ($\chi^2 = 11.6$; $p < 0.001$). Of the separate groups, it is significantly higher only in the duodenal-ulcer group. These figures also show that it occurs about as frequently in the acute-lesion group as in the chronic group. It is usually not nearly so grave an omen in the acute-lesion group, although even in these cases recurrent hemorrhage may be a threat of life.

Influence of Site and Chronicity of Ulcer

The mortality in relation to the site and chronicity of the ulcer is shown in Table 6.

The apparently higher mortality in the chronic-gastric-ulcer group than in the rest of the series, taken as a whole, is not quite statistically significant. However, the age and sex distribution is not quite comparable in the gastric- and duodenal-ulcer groups; the duodenal-ulcer group has 14 patients over 70, as opposed to 1 in the gastric-ulcer group.

Influence of Age and Sex

The mortality according to age and sex is shown in Table 7.

The differential death rate, expressed as a percentage of the cases in each group, appears not to support convincingly the contention that mortality is closely related to the age of the patient, particularly in patients of 50 and over. The comparatively low mortality in the 70-79 age-group may be explained by a fortunate run of less severe cases, which a longer series would even out. The 3 deaths in the 40-49 age group were in men of 45, 45 and 49, and were all postoperative. It is reasonable to inquire whether these 3 patients had anything in

TABLE 4. Analysis of the 15 Deaths

Case #, sex, age	Diag. group ^a	Prev. hem.	Time of death after admission	Hematemesis or melena	Blood given (cc.)	Brisk recur- rent hem.	History of dyspepsia (yr.)	Complications ^b			Operation for bleeding and time after admission	Postmortem findings
								A	B	C		
6 M, 67	CG	+	48 da.	HM	7000	+	3 yr.	++++	-	+	-	Chronic G.U. on lesser curve. Pancreas eroded. R. gastric artery involved
30 M, 65	D	+	11 hr.	M	500	+	30 yr.	+	-	-	-	Not done
40 M, 45	CG	+	22 da.	M	1000	-	5 yr.	++	-	-	10 da.	Herniation of small gut through hole in greater omentum. Peritonitis. Bron- chopneumonia.
42 M, 75	D	-	10 hr.	H	1500	+	3 wk.	+	-	-	-	Chronic D.U. on posterior wall. Eroded artery seen. Thrombosis in veins of r. leg. Small pulmonary emboli.
44 M, 45	CG	+	38 da.	H	3500	+	2 yr.	+	-	-	30 da.	General peritonitis from leak on lesser curve. Severe benign hypertensive changes in kidneys.
46 M, 56	D	-	8 da.	H	4500	+	20 yr.	++	++	+	-	Chronic adherent D.U. on posterior wall. Artery found. Second D.U. on anterior wall.
55 M, 57	CG	-	1½ hr.	M	Less than 1 mo.	++	-	-	-	2 chronic D.U.'s on posterior wall, artery seen in one. Chronic bronchitis and em- physema.

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71 F, 73	I	-	10 da.	M	-	+	-	-	-	-	Not done
72 M, 61	D	+	22 da.	HM	3000	+	6 yr.	-	+	-	Not done
76 M, 52	CG	+	Less than 1 da.	H	2500	+	12 yr.	-	-	-	Thoracic stomach, with large lesser curve G.U. Probable terminal aspiration of vomit. Artery seen.
124 M, 67	CG	-	19 da.	M	8500	+	15 yr.	-	-	-	Penetrating lesser curve G.U. Artery seen.
129 M, 60	CG	-	23 da.	HM	500	-	2 yr.	+	+	+	Perforated G.U. Eroded artery seen. Bronchopneumonia. Multiple small pulmonary emboli.
138 M, 58	I	-	8 da.	HM	6000	+	33 yr.	+	-	-	Not done
141 M, 49	D	-	3 da.	M	7000	+	17 yr.	+	-	-	2 da. Not done
163 M, 62	D	-	7 da.	HM	12000	+	4 yr.	-	+	+	3 da. Chronic D.U. Thrombosis of superior mesenteric vein. Bronchopneumonia. Artery seen.

^a CG = Chronic gastric ulcer. D = Duodenal ulcer. I = Incompletely investigated group.

^b A = Unrelated diseases, present on admission. B = Complications of the ulcer. C = Arising after admission, but not directly associated with the ulcer.

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TABLE 5. Effect of Brisk Recurrent Hemorrhage on Prognosis

	Chronic gastric ulcer	Duodenal ulcer	Acute lesion group	Incomplete investigation	Totals
No. patients	15	26	10	5	56
No. deaths	4	6	0	2	12
Mortality rate (%)	26.6	23.0	0	40	21.4
Mortality rate (%)—entire series	18.7	9.9	0	16.7	9.7

TABLE 6. Mortality in Relation to Site and Chronicity of Ulcer

Site	No. cases	Deaths	
		No.	%
Chronic gastric ulcer	32	6	18.7
Duodenal ulcer	71	7	9.9
Acute lesion group	39	0	0
Incomplete investigation	12	2	16.7
TOTAL	154	15	9.7

TABLE 7. Mortality According to Age and Sex

Age group	Cases			Deaths			Mortality rate (%)
	M	F	Total	M	F	Total	
10-19	1	..	1	0	0
20-29	4	1	5	0	0
30-39	8	1	9	0	0
40-49	20	7	27	3	..	3	11.1
50-59	33	9	42	4	..	4	9.5
60-69	32	9	41	6	..	6	14.6
70-79	20	7	27	1	1	2	7.4
80-89	2	..	2	0	0
TOTAL	120	34	154	14	1	15	9.7

common with each other and with the other fatal cases, and it is shown below that there is an association between mortality and serious complicating disease.

The higher mortality in older patients is not associated in the present series with a greater length of ulcer history, with a greater incidence of previous hemorrhage, with a greater total blood loss (as measured by blood transfused) or a greater risk of brisk recurrent hemorrhage in hospital.

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Effect of Complicating Diseases

Lewin and Truelove point out that, because there is an increasing hazard with age in perforated peptic ulcer as well as in bleeding peptic ulcer, the cause of the increased mortality in older people lies in "changes in the whole organism." Ferguson and Wyman give figures which are at least suggestive that this higher mortality is caused by the increasing frequency of severe complicating disease with age. To investigate this possibility, complications have been classified into three groups:

- A. *Those present on admission, but caused neither by the ulcer nor by the hemorrhage*; for example, bronchial asthma, chronic nephritis, cardiac failure.
- B. *Complications of the ulcer*, whether present on admission (e.g., pyloric stenosis) or occurring later (e.g., perforation).
- C. *Complications arising after admission, but not directly associated with the ulcer*; for example, acute retention of urine, broncho-pneumonia, venous thrombosis of leg.

The incidence of these three types of complicating disease in relation to age is shown in Table 8.

These figures refer to individual complications, not to patients, some having more than one. This difference in those under and over 50 is statistically significant ($\chi^2 = 14.2$; $p < 0.001$).

Table 9 shows the relation of complications and age to mortality. These figures refer to *patients*. The differences are statistically signifi-

TABLE 8. Incidence of Complications According to Age

	Complication group			Total	Per patient
	A	B	C		
No. in patients under 50	8	1		9	0.21
No. in patients over 50	44	12	8	64	0.59
TOTALS	52	13	8	73	0.47

TABLE 9. Effect of Complications on Mortality According to Age

Age group	With A, B, or C		Without A, B, or C	
	Total	Deaths	Total	Deaths
Under 50	8	3	34	
50 and over	51	11	61	1
TOTALS	59	14	95	1

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TABLE 10. Relation Between Complicating Diseases, Brisk Recurrent Hemorrhage and Mortality

Group	Under 50		50 and over	
	Cases	Deaths	Cases	Deaths
(a) Cases with neither brisk recurrent hemorrhage nor any complications	27	0	42	0
(b) Cases with brisk recurrent hemorrhage alone	7	0	21	1
(c) Cases with one or more complications, but not brisk recurrent hemorrhage	5	1	24	2
(d) Cases with one or more complications and brisk recurrent hemorrhage	3	2	25	9

cant, ($p = 0.007$ for those under 50 and approximately 0.001 for those over 50).

Even when allowance is made for the fact that not all these associated or complicating diseases can be considered as quantitatively equal, there is clearly a relationship between complicating diseases and the rising mortality with increasing age. The 3 patients under 50 who died all had a serious associated disease. One had severe benign hypertension, with low renal function, one had benign hypertension, though not so severe, and the third had gross emphysema, with clubbing of the fingers. These complications distinguished these 3 patients from all but 2 of the remaining 24 of those in the 40-49 decade.

Relation Between Complicating Diseases, Hemorrhage, and Mortality

In those under 50, the deaths in (d) are significantly greater than in (a) but the numbers in (b) and (c) are too small for comparison. In those over 50, the deaths in (d) are significantly greater than in (a), (b) or (c), ($p < 0.001$). The same applies to the total combined figures for all ages. The 1 fatal case in which neither brisk recurrent hemorrhage nor a complicating disease was observed clinically was a man of 57, who died 25 minutes after his arrival at the hospital in a moribund condition, and was found at necropsy to have severe emphysema and chronic bronchitis, as well as two chronic peptic ulcers on the posterior wall of the duodenum, from one of which he had bled to death.

TREATMENT

Almost all the patients were admitted under one or other of two medical firms, in approximately equal numbers. There was no unified

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TABLE 11. Emergency Operations Performed Because of Bleeding

Case #, sex, age	Group ^a	Days after admission	Operation	Result
40 M,45	CG	10	Partial gastrectomy	Patient died 10 days after operation from strangulated loop of gut through hole in greater omentum
44 M,45	CG	31	Partial gastrectomy	Died 9 days later—general peritonitis following leak on lesser curve
64 M,60	D	18	Partial gastrectomy	Recovered
65 M,53	CG	4	Partial gastrectomy	Recovered
90 M,57	D	3	Partial gastrectomy	Recovered
104 M,68	D	7	Partial gastrectomy	Recovered
121 M,60	D	9	Partial gastrectomy	Recovered
131 M,60	CG	6	Partial gastrectomy	Recovered
141 M,49	D	2	Partial gastrectomy	Died next day—no post-mortem
149 M,52	D	3	Partial gastrectomy	Recovered
157 M,56	Acute- lesion group	8	Gastrotomy, with undersewing of possible bleeding point	Recovered
163 M,62	D	3	Middle colic artery tied—transverse colostomy	Died next day. Chronic D.U. Thrombosis of superior mesenteric vein. Bronchopneumonia.
164 F,63	Acute- lesion group	15	Partial gastrectomy	Recovered
169 M,52	CG	2	Partial gastrectomy	Recovered

^a CG = Chronic gastric ulcer. D = Duodenal ulcer.

^b Had had gastroenterostomy 11 years before hemorrhage.

policy of treatment, but the approach did not differ greatly between the two firms. Feeding has inclined towards liberality, without approaching the full-scale Meulengracht diet. Of the 154 patients, 107 had a blood transfusion. No patient died because there was not enough compatible blood available. There was no agreed policy about surgery, but each case was considered strictly on its merits, the tendency being to operate on patients with a known chronic ulcer, whose bleed-

ing was not responding to medical treatment. Two patients had emergency operations in which no chronic ulcer was found. The patients who were operated on because of bleeding are set out in Table 11.

In retrospect, there were no patients where operation seemed to have been ill-advised. Of the 11 patients who died without operation, there is only one in whose case it is tempting to suppose that surgery might have influenced the result. Of the remainder, either death occurred very soon after admission, or there were one or more complicating diseases serious enough to make operation impracticable.

DISCUSSION

This series of patients is in many ways similar to those reported recently in England and in Northwest Europe. For example, Fraenkel and Truelove give an account of the cases in the Radcliffe Infirmary in a five-year period which overlaps our 20-month period at either end. The rate of admission of an average of 12 patients a month is approximately the same as in Addenbrooke's Hospital. The proportion of patients over 50, though high, is a little less than in Cambridge. The mortality is slightly lower (8.3 per cent). The policy about surgery appears to have been similar, and operation, as in most of the present series (see Table 11), confined to partial gastrectomy.

The most striking changes in the history of the patients treated in hospital in the last 30 years are the almost complete disappearance of the acute gastric ulcer of young women as a cause of serious gastric bleeding, and the emergence of the group of patients of late middle-age and older with chronic ulcers. This has presented a problem whose developing magnitude was not realized soon enough in the 1930's, and such patients now constitute the great majority of the cases. That they have a worse prognosis than those under 50, other things being equal, is now well known, and this higher mortality appears to be associated with a greater incidence of associated diseases, or complications of the ulcer, though it must be admitted that there are various general bodily changes in the elderly whose effects cannot be measured, nor at present even precisely defined. The results of treatment, in terms of percentage mortality, compare favorably with other recent comparable series, when the fact that 78.0 per cent of the 154 cases were aged 50 or over is taken into account. The series is too small to draw definite conclusions about the place of surgery, but in general, it may be said that a policy of selective surgery, with close

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cooperation between physician and surgeon, appears to have been justified.

SUMMARY

1. An analysis is made of 170 consecutive admissions for hematemesis and melena in a period of 20 months in 1950-52. Of these, 154 cases are regarded as being proved or probable cases of peptic ulcer. The mortality in these 154 cases was 15 (9.7 per cent).

2. The over-all picture of the peptic ulcer cases is in accordance with the present trends of an increasing proportion of middle-aged and elderly men, and confirms the almost complete disappearance of the acute gastric ulcer of young women as a source of serious gastric bleeding.

3. There were 34 cases of probable peptic ulcer which were "X-ray-negative." The different sex distribution, the short dyspeptic history, the good prognosis, and the clinical history of hematemesis rather than melena are all adduced as reasons for considering that most of these patients had shallow acute gastric ulcers.

4. The mortality is related to the total blood loss, and is associated with the occurrence of brisk recurrent hemorrhage after admission to hospital. Of other factors investigated, the most significant one was the presence or development of other diseases, or of complications of the ulcer.

5. This, as well as the comparative smallness of the number of cases, is thought to account for some anomalies in the age distribution of the deaths.

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ACTH and Cortisone Therapy in Ulcerative Colitis

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THE first reports of treatment of acute and chronic ulcerative colitis by steroid hormones appeared in 1950.¹⁻³ Since then, many other papers⁴⁻¹⁶ have described striking improvement in critically ill patients. Coincident with this markedly beneficial effect in some patients, certain serious complications have been described in others,¹⁷⁻²⁰ notably hemorrhage and perforation in the stomach and in the bowel. We have had the opportunity of treating this disease with the same agents, and have noted similar complications. The purpose of this communication is to summarize our experiences with steroid therapy in ulcerative colitis on the wards of the Mount Sinai Hospital during the years 1952-54.

The difficulty of evaluating the effect of steroid therapy, or of any other single agent was recognized in view of the frequently unpredictable course and the tendency of the disease to spontaneous remission or severe relapse. A change in environment and simple supportive therapy may be beneficial in some patients, and of little avail in others. However, it is of value to assess the results in any group of patients in which a major therapeutic agent such as ACTH or cortisone has been used.

MATERIAL

ACTH and cortisone were used in 27 patients (about one third the number of cases of ulcerative colitis in the period from 1952-54). The majority of these patients were severely ill and had not responded to the usual supportive measures, which included bed rest, low-residue diet, vitamins, whole-blood transfusions, intravenous fluids and electrolytes, hematinics, opiates, sulfonamides, antibiotics, anti-

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spasmodic drugs and occasionally psychotherapy. Some of the patients had colitis of fairly recent origin, while others were victims of chronic, long-standing colitis. The severity of their illness is emphasized by the relatively high incidence of serious complications which necessitated surgery (9 cases). In all cases the diagnosis was confirmed by sigmoidoscopic examinations and barium-enema studies, and by systematic exclusion of pathogenic organisms, such as amebae, in the stool.

Among the 27 patients, there were 9 males and 18 females, ranging in age from 17 to 60 years. The duration of the disease varied from 3 weeks to 4 months in the acute cases, and from 9 months to 16 years in the chronic patients.

DIAGNOSTIC METHODS AND FINDINGS

All patients were subjected to sigmoidoscopy and complete gastrointestinal x-ray studies as well as extensive laboratory surveys. Twenty-two cases showed typical changes of ulcerative colitis on endoscopic examination varying from engorgement and friability to the most advanced destruction, with deep ulceration, mucopurulent exudate, and pseudopolypi. Five cases appeared to have a normal sigmoid mucosa, and these were classified as proximal colitis.

All patients showed definite changes of ulcerative colitis on barium enema, in varying degree, manifested by more or less extensive areas of mucosal destruction, ulcerations, spasm, absence of haustral markings, and shortening and lack of distensibility of the colon.

Blood Studies

Secondary anemia was present in almost all patients (22 had a hemoglobin level between 6.7 and 12 Gm./100 cc.), and a varying degree of leukocytosis with shift to the left was an almost constant finding. Leukopenia was present in a few patients. The anemia was an indication for blood transfusions. No particular significance was attached to the leukocytosis as a guide to the extent or progress of the disease. In fact, in those cases in which leukocytosis might have been present to suggest a surgical complication such as perforation, elevation of the white blood count was not demonstrated.

Hypoalbuminemia and relative hyperglobulinemia were present in practically all cases and did not vary appreciably in response to blood transfusions and protein supplements. The erythrocyte sedimentation rate was markedly elevated in all cases. Changes towards normal values of the sedimentation rate and the serum albumin usually paralleled the clinical improvement.

Stool Examinations

All the patients had multiple stool examinations, which showed the presence of blood (occult or gross), and absence of intestinal parasites and bacterial pathogens. One patient with a past history of treated amebiasis did not show amebae, even in the postcolectomy pathologic specimen.

THERAPEUTIC REGIMEN

No uniform dosage schedule was followed in all the cases. Use of ACTH or cortisone was usually dictated by the patient's condition on the one hand, and by the predilection of the service on the other. Still, a procedural trend was discernible.

At the onset, extremely ill patients received 40–100 u./day of intravenous ACTH, or 100 mg./day of intravenous hydrocortisone, or multiple doses of intramuscular aqueous ACTH (80–100 u./day). The aqueous steroids, whether administered intravenously or intramuscularly, were favored because of their greater effectiveness and a more predictable action than the oral or gel forms. Any one of these drugs administered in adequate dosage usually effected a dramatic improvement in the patient's general condition, with subsidence of toxemia, improvement in hydration, decrease in temperature and pulse rate, change in mental attitude, and increase in appetite. Pain and diarrhea were relieved more slowly.

After 7–27 days of intravenous steroid therapy most of the patients were switched either to the intramuscular ACTH gel, 80–100 u./day, or to oral cortisone (Compound E) tablets, starting with 50 to 33 mg./day. In many of the less severely ill patients, one or both of these drugs were used. Only 1 patient had a course of hydrocortisone (Compound F; initial dosage 160 mg./day). No definite superiority of either ACTH gel or cortisone was apparent, and either one of them acted favorably in certain cases while failing in others. However, ACTH gel was slightly more efficacious in initiating a remission, while cortisone seemed to be more beneficial in the less severe cases. In 2 cases in which cortisone was ineffective, ACTH gel produced an excellent result in one and none in the other. One patient did not show any improvement on ACTH (low dosage), but responded well to large doses of cortisone.

The extracolonic manifestations or complications of ulcerative colitis encountered in our series (erythema nodosum, erythema multiforme, arthritis, arthralgias, and phlyctenular conjunctivitis) showed a uniformly good, and often prompt, response to any form of steroid therapy. In 2 cases these manifestations were the primary indications for

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the use of hormones. The concomitant improvement in the colitis warranted their prolonged administration, until a remission was obtained.

RESULTS

In our series of 27 patients, with a total of 34 hospital admissions during which steroid therapy was administered, the results were evaluated for each hospital admission separately as shown in Table 1.

In 6 cases of acute ulcerative colitis, 3 remissions and 1 temporary improvement were achieved. One severely ill patient who had received an adequate course of steroids did not show any improvement. The drug was discontinued because of an intercurrent pneumonia. Another critically ill patient suffered a perforation of the diseased colon while on ACTH gel.

In the cases of chronic ulcerative colitis (28 hospital admissions) the results were better in the less severely ill patients than in the extremely sick. Thus, in 13 moderately severe cases, 10 remissions and 3 tempo-

TABLE 1. Results of Therapy

Type of colitis	No. cases	Sex of pt.			Results of therapy			
		M	F	Remission	Temp. improved	Un- changed	Wors- ened	Perfor- ation
Acute ulcerative								
Proximal (right- sided)								
Moderately severe	2	..	2	1	1
Universal								
Moderately severe	2	2	..	2
Severe	1	..	1	1
Fulminating	1	..	1	1
TOTALS	6	2	4	3	1	1	..	1
Chronic ulcerative								
Proximal (right- sided)								
Moderately severe	2	2	..	2
Severe	1	..	1	1
Distal (left-sided)								
Moderately severe	1	..	1	1
Universal								
Moderately severe	13	4	9	10	3
Severe	8	2	6	3	2	2	1	..
Very severe	3	..	3	1	..	1	..	1
TOTALS	28	8	20	18	5	3	1	1

rary improvements were achieved. In 8 severe cases there were only 3 remissions; 2 patients had temporary improvement, 2 showed no change, and 1 became worse. Still poorer results are shown by the 3 severely sick patients—1 remission, 1 patient's course was uninfluenced by the drug, and 1 suffered perforation of the colon.

Apparently age and sex were not material in assessing the value of therapy.

Side Effects and Complications

The observation made by Soffer and associates,²² in their report on lupus erythematosus treated with steroids, that the underlying disease process predisposes to specific side effects seems to be confirmed by our findings.

Side effects of the steroids were noted in 11 cases, and ranged from mild (Cushing facies, slight edema, acne, aggravation of diabetic state) to severe (perforation of the colon without the usual signs of peritonitis). Postoperative shock due to adrenal exhaustion occurred in 1 patient who received ACTH for 23 days before operation. In 1 very ill patient with a moderately distended and tender abdomen a perforation of the colon was diagnosed 18 hours after intravenous ACTH (total dose 40/u.) was started. The causal relationship between ACTH administration and perforation was not satisfactorily established in this case, and might have been coincidental. This patient had an emergency ileostomy and subtotal colectomy performed, at which time these perforations (two old and one fresh) were found. Her postoperative course was relatively benign.

Except for severe complications (perforation, spread of infection, delay in healing of skin ulcers, bleeding), the relatively minor effects did not interfere with continued administration of the particular steroid in any of our patients. The more ominous side effects (hypertension, convulsions, congestive failure, metabolic alkalosis, peptic ulcer) noted during the treatment of lupus²² and rheumatoid arthritis were not present in our series.

The glycosuria of the patients who received massive doses of steroids and did not have preexisting diabetes mellitus did not present a problem in management. In 2 cases even with markedly diabetic glucose tolerance curves, no ketosis or ketonuria were encountered.

Only 1 of our patients suffered hemorrhage during the course of therapy. She bled on the eighth day after the last dose of ACTH, with cessation after transfusion, and later was operated upon during a period of remission.

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Cases Requiring Surgery

Nine of the studied cases required ileostomies and colectomies. Two were operated upon because of perforations, and 1 for intractability while still receiving ACTH. The 6 patients were explored after steroids were discontinued because of intercurrent infection, delay in healing of a skin ulcer, or because of intractability. There were no deaths in this surgically treated group. Although we cannot generalize for all the patients operated on, we feel that the preliminary steroid therapy caused an improvement in their general condition or a remission, thus permitting operation during a period of relative quiescence. The survival of the patients with open perforations was ascribed to early diagnosis and immediate surgery.

Cases Requiring Psychotherapy

Nine patients were given psychotherapy in conjunction with steroids. Two of them underwent surgery—one very severe case because of intractability, another because of hemorrhage. The 7 others, all moderately severe cases, improved remarkably on superficial psychotherapy and steroids. One of these patients who was subjected to three courses of this type of combined therapy showed good symptomatic response and marked improvement in her general condition on each of her hospitalizations, with remissions lasting 6–12 months. However, despite the period of quiescence, the disease process in the colon was not interrupted, as demonstrated radiologically and sigmoidoscopically. The favorable experiences with steroids at the time these patients were receiving psychotherapy parallels that reported by Saver *et al.*²⁴

Follow-up

Of the 27 patients, 6 must be classified as not having been helped by steroid therapy. Out of 21 cases in whom remissions were obtained 3 were lost to follow-up. Six cases relapsed within $4\frac{1}{2}$ –14 months (average 10 months) from their discharge from the hospital. One patient, apparently in symptomatic remission for 2 months, was forced to undergo colectomy because of a slow perforation with pericolic abscess. The 11 remaining cases were followed for 2–18 (average 7.5) months, during which none of them complained of symptoms, and all were able to resume their occupations.

DISCUSSION

The adrenocortical steroids are valuable drugs in the treatment of ulcerative colitis. It would seem that their effectiveness is superior to

that of any other single drug used for this disease. In spite of that, neither our studies nor the previously published reports have shown that cure of ulcerative colitis can be achieved by their administration. The evidence from this survey would imply that steroid therapy will induce or hasten the onset of a remission in some patients who do not respond to conventional medical treatment, and even to psychotherapy, but that it is not effective in all patients. We were unable to define criteria by which the response in any one patient could be predicted, neither could we marshal any evidence to support conflicting findings that cortisone and ACTH were superior in acute cases^{6, 18} or in chronic ulcerative colitis, as described by others.⁴

Hazards of Administration

It is important to recognize that the administration of ACTH and cortisone is fraught with certain hazards. Of paramount importance is the danger of perforation of the diseased colon. This complication is not very rare (two of our 27 patients, an incidence of 7.4%) and has been repeatedly reported in the literature.^{5, 17, 20} In order to forestall this danger, we have felt that it is important to refrain from the administration of steroids if signs of peritoneal irritation or x-ray evidences of deep ulceration are present. In the severely ill patient this danger is real.

Dosage

An adequate dosage administered over a relatively long period of time is essential for a good therapeutic response to steroids. The dosage level must be adapted to the needs of the patient, the severity of the disease, and the response of the individual to the drug. Too rapid premature reduction in the dose or premature discontinuance is often followed by relapse. The optimal maintenance level must be established by trial and error.

Since doses of 600–800 mg. of cortisone have been used in some previously fatal conditions (pemphigus vulgaris, lupus erythematosus, etc.), it is not unusual to administer doses of 300 mg. of cortisone per day for ulcerative colitis. It has been the experience of Kirsner and Palmer¹¹ as well as ourselves that these higher levels are more effective in inducing a remission than the lower dosages. Some of our patients who relapsed after having had a temporary response to doses of 100 mg. of cortisone had prolonged remissions after another higher dosage trial.

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Mechanism of Action

The mechanism of the beneficial action of steroids in ulcerative colitis is not clear. Boland²³ suggested that oversensitivity of mesenchymal tissue is inhibited. Alterations in enzyme systems, tissue permeability, and the mechanisms involving hyaluronidase have been invoked^{11, 16} but without supporting evidence as yet. Other authors have argued that steroids are beneficial entirely by their euphoria-inducing effect. This might be an important factor, but as Dick and Beckett⁶ have pointed out, the improvement, such as fall of temperature, is dramatic, and occurs coincidentally with,¹¹ and sometimes before, the change in mental outlook. Ruffin¹⁴ and Elliott and Gian-siracusa⁷ are convinced that the favorable response is related to antiinflammatory effects.

CONCLUSIONS and SUMMARY

1. Twenty-seven patients with acute or chronic ulcerative colitis who did not respond to conventional medical therapy were treated with ACTH, cortisone, or hydrocortisone.

2. Steroids were found to be of value in inducing or hastening the onset of a remission in 21 out of 34 trials. No evidence for a curative effect was seen. Extracolonic manifestations of ulcerative colitis (erythema nodosum, arthritis, conjunctivitis) reacted more promptly to therapy than did the colonic disease.

3. No death occurred during treatment. Two perforations and 1 severe hemorrhage were encountered.

4. Nine patients ultimately required surgery for intractability of symptoms and lack of response to therapy, including steroids, and their surgical course was uneventful.

5. Caution in administration and careful selection of patients for steroid therapy is advised in view of the danger of serious side effects.

6. The theories concerning the mechanism of action of steroids in ulcerative colitis have been discussed.

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Acquired Hiatus Hernia

COSTANTINO ZAINO, M.D., and MAXWELL H. POPPEL, M.D.

EARLY DIAGNOSIS, classification, and the management of hiatus hernia have of late gained impetus because of the increased incidence of this condition and the frequency of complications, particularly in the sliding type.

The esophagogastric junction still presents to the radiologist, as well as to the anatomist, endoscopist, and clinician, an area difficult for gastrointestinal diagnosis, because of inadequate knowledge of the closing mechanism. However, Lerche¹ has described a "gastroesophageal segment of expulsion" consisting of the structures between the lower esophagus and the stomach which are concerned with this mechanism. Recent roentgenologic studies by us seem to confirm Lerche's findings. In addition we reviewed the normal roentgen anatomy (Fig. 1) of this area in terms of these newer concepts and summarized the criteria for the diagnosis of hiatal insufficiency and hernia.²

In order to further clarify this subject we will now review the entire problem of acquired hiatus hernia including classification, etiology, clinical considerations, complications, roentgen differential diagnosis, and treatment. Outline drawings of the various types of hiatal insufficiency and hernia based on our previous study are included as an aid in the diagnosis.

There has been considerable confusion as to the classification of hiatus hernia. The term "sliding" is an unfortunate one since actually all hiatal hernias slide above the level of the diaphragm. But since the terms "sliding" and "paraesophageal" are widely used we are retaining them but defining them in accordance with our concept of the underlying abnormality. The roentgenologic classification which follows will define three types of sliding hernia. The importance of the subclassifications is to convey as much information as possible to the clinician. There are also early changes which precede the actual appearance of the hernia as defined in the following pages. This is referred to as "insufficiency."

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ROENTGENOLOGIC CLASSIFICATION

Sliding Hiatus Hernia

A sliding hiatus hernia is defined as the upward migration of the abdominal segment of the esophagus and esophagogastric junction to above the level of the diaphragm, through the esophageal hiatus.

Concentric or Short-Esophagus Type

This is defined as a gastric herniation through the esophageal hiatus (Fig. 2), with the esophagogastric junction above the diaphragm and at the center or apex of the herniated pouch, and with foreshortening of the esophagus. Before this actually takes place there are three preliminary progressive stages of insufficiency:

Stage A. Dilated, persistent and slowly emptying phrenic ampulla.

Stage B. High phrenic ampulla, and vestibule mostly above the right crus of the diaphragm.

Stage C. Gastroesophageal junction at the esophageal hiatus (Fig. 3).

Before one can be sure an insufficiency is present other causes producing a persistent or sluggish emptying of the phrenic ampulla must be excluded. These include a small esophageal hiatus, a fixed diaphragm, pleural adhesions, and so on. Such findings have also to be evaluated in terms of the habitus of the patient. For example, in a

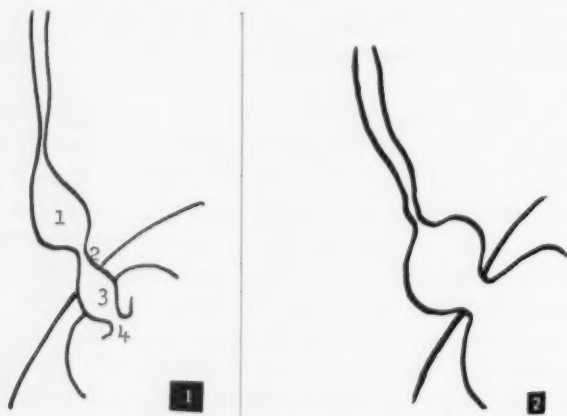


Fig. 1. 1, phrenic ampulla; 2, inferior esophageal sphincter; 3, gastroesophageal vestibule; 4, constrictor cardia. Note: All drawings were copied from radiograms taken in the prone right anterior oblique position and in full inspiration. Fig. 2. Sliding concentric hiatus hernia.

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Fig. 3. Sliding hiatus insufficiency, Stages A, B, and C.

hypersthenic person the gastroesophageal junction may be relatively high. A persistent phrenic ampulla due to a loss of muscular tone of the esophagus seen in older individuals should be considered as the first stage of insufficiency in that a predisposing factor to the formation of a sliding-type hernia is obviously present.

Redundant-Esophagus Type

This can be defined as a sliding hernia with the herniated stomach curled to one side of the esophagus above the diaphragm (Fig. 4). In this type of hernia the esophagus is redundant. It is probably most frequent in older individuals who have lost some of the elastic-tissue tonicity of the entire esophagus. The preliminary stage of insufficiency is a redundant esophagus with the gastroesophageal junction at the esophageal hiatus. Subsequently the herniated stomach slides to one side of the redundant esophagus.

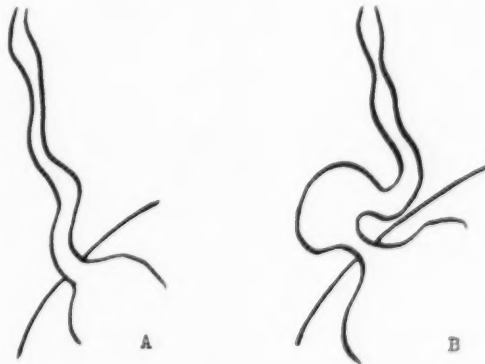


Fig. 4. A, sliding hiatus insufficiency of the redundant-esophagus type. B, sliding hiatus hernia of the redundant-esophagus type.



Fig. 5. A, normal stomach with a high cardial pouch. B, sliding hiatal insufficiency with a paraesophageal component. C, sliding hiatus hernia with a paraesophageal component.

Sliding Hiatus Hernia with Paraesophageal Component

This is a sliding hernia in a stomach with a high cardial pouch (Fig. 5). There is an upward migration of the esophagus, gastroesophageal junction, and cardial pouch as a unit, to the level of the esophageal hiatus and above. At first, or in the stage of insufficiency, only part of the cardial pouch protrudes off to one side of the diaphragm. Eventually more of the cardia protrudes through, and the gastroesophageal junction is at the esophageal hiatus. This type of hernia may be difficult to differentiate from the true paraesophageal hiatal hernia. The level of the gastroesophageal junction and the configuration of the cardia are the differentiating factors.

Paraesophageal Hiatus Hernia

Paraesophageal hiatus hernia is defined as herniation of the stomach to one side of the esophagus through the esophageal hiatus (Fig. 6). The gastroesophageal junction is in its normal position. A preliminary stage of insufficiency may be noted as an occasional knuckle of cardia

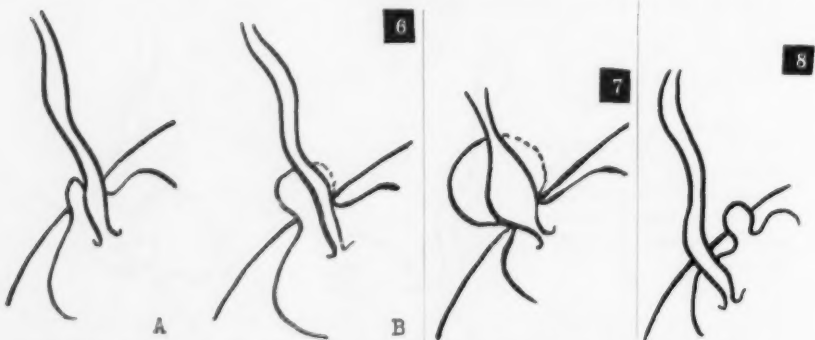


Fig. 6. A, paraesophageal hiatal insufficiency. B, paraesophageal hiatus hernia. Fig. 7. Double-ring shadow. Fig. 8. Sweet's-type paraesophageal hernia.

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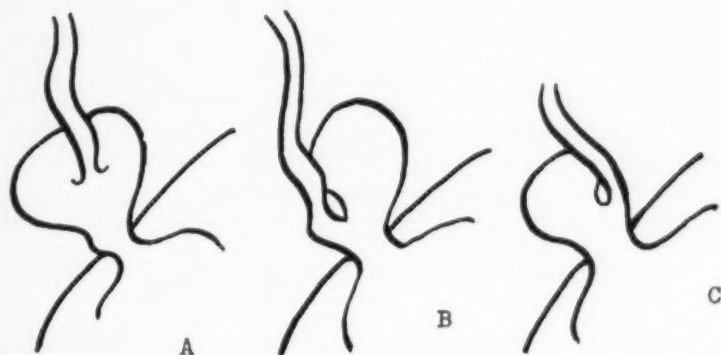


Fig. 9. Mixed-type hiatus hernia. A, B, and C, various mixed types.

or fundus protruding to one side of the esophageal hiatus. As this condition progresses the herniated pouch becomes larger and more persistent but the gastroesophageal junction is still in its normal position. This diagnosis is facilitated if the "double ring" shadow can be seen (Fig. 7). This is a roentgenologic sign produced by the shadows of the dilated vestibule and herniated stomach pouch superimposed on each other. Both the vestibule and herniated pouch are somewhat dilated because of the sluggish emptying due to compression on the esophagus by the herniated pouch at the esophageal hiatus, especially in full inspiration. Mucosal pattern transparency is essential here to distinguish the two separate structures.

This type hernia must be differentiated from Sweet's type of paraesophageal hernia,¹² which is not a true hiatal hernia but a herniation through a defect adjacent to the esophagus (Fig. 8). However, occasionally the defect may be so close to the esophagus that differentiation is roentgenologically impossible.

Mixed Type

The mixed type of hernia has component findings of both sliding and the paraesophageal variety (Fig. 9).

ETIOLOGY

Acquired hiatus hernia is the most common of the diaphragmatic hernias. In the majority of cases there is probably an underlying congenital weakness, such as an unusually wide esophageal hiatus or defective phrenoesophageal membrane. The position, direction, and configuration of the esophageal hiatus are found to vary considerably,

so that possibly even additional factors may be responsible for the eventual widening or break through of this opening. Occasionally a preformed pocket may be present alongside the esophagus (persistent pneumoenteric recess) which offers a potential opening to the formation of a paraesophageal hernia.³ The hernia itself seems to be precipitated by a number of factors working together or separately:

- Increased abdominal pressure, as in pregnancy.
- Decreased intrathoracic pressure, as in chronic pulmonary diseases.
- Obesity, resulting in widening of the hiatal ring from fatty deposits.
- Neurogenic factors producing frequent or sustained esophageal spasm, as in peptic ulcer or gallbladder disease.
- Atrophic changes due to senility, resulting in the loss of elasticity of the elastic tissues and general relaxation of the structure in the region of the lower esophagus.

Esophageal Spasm

Spasm of the esophagus is probably the most important of these factors in younger individuals. Many gastrointestinal disturbances reflexly cause abnormal contraction of the esophagus. If this is allowed to go on unchecked over a relatively long period, in individuals with a pre-existing congenital weakness in the anchoring mechanism of the lower esophagus, it seems reasonable to assume that a sliding type of hiatus hernia will develop. In our experience we have seen obvious cases of sliding hiatus hernia demonstrable only during periods of spastic contractions of the esophagus. In other cases the hernia was demonstrable only during periods of activity of a peptic ulcer. A sliding type of hiatus hernia has also been demonstrated during spasm secondary to an esophageal diverticulum. It may be interesting to note here that hiatus hernia may in turn be a cause of spasm of the esophagus, so that at times it may be difficult to decide the primary cause of irritation, especially if other gastrointestinal conditions co-exist. This is particularly true in older individuals where hiatus hernia is much more frequent and usually larger.

CLINICAL CONSIDERATIONS

Hiatus hernia well deserves the title of "the great masquerader." In older patients a hiatus hernia is usually discovered on routine roentgen examination taken chiefly to rule out the presence of a neoplasm. These patients usually have a variety of gastrointestinal com-

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plaints. For how many years the hernia has been present and to what extent the symptoms are related to the hernia may be at times impossible to determine, and in certain patients this may present a difficult diagnostic and therapeutic problem.

Hiatus hernia may be asymptomatic. This is particularly true in its early stages; and in its early stages, without special roentgen studies, hiatal insufficiency and hernia may not be recognized. Yet knowledge of the presence of this defect may clarify subsequent appearance of symptoms. In addition, precautionary measures may be taken to forestall complications and retard progressive enlargement of the hernia.

Symptoms

The symptoms of hiatus hernia may be vague and variable. They may be digestive, circulatory, and respiratory in character. As in the case of a neoplasm, the appearance of symptoms may indicate the presence of a relatively large hernia or the onset of complications.

Pain

One of the chief complaints is substernal discomfort or pain, usually relieved by belching and aggravated only on lying down. The pain may at times be quite severe and "viselike." It may resemble anginal pain and may be confused with coronary disease. It may occur following exertion but usually occurs after a heavy meal and while wearing a tight corset or abdominal binder.

There may also be the typical cardiac neurogenic radiation of pain, but no drop in blood pressure or any EKG or blood-picture changes are found. In hiatus hernia the duration of these symptoms usually dates back many years, yet there may be little or no evidence of heart disease. The diagnosis of the hiatus hernia may be obscured by the coexistence of other conditions, including coronary sclerosis. A large hiatus hernia compressing the heart may produce cardiac arrhythmia, tachycardia, dyspnea, and even cyanosis.

Heartburn

Heartburn is another important symptom of hiatus hernia. It is due to distention of the lower esophagus by regurgitated food secondary to alterations of the neuromuscular activity of the esophagus producing reverse peristalsis. It is very important to be able to demonstrate regurgitation roentgenologically in the presence of a sliding hiatus hernia. Persistent regurgitation will lead to reflux esophagitis and may require early surgical intervention, especially in younger pa-

tients. But heartburn also occurs in many other conditions and is quite common after excitement and undue stress, or following a heavy meal and overindulgence in alcoholic beverages. At any rate, persistent heartburn in a patient with hiatus hernia is a warning signal of trouble ahead.

Anemia and Other Symptoms

Hiatus hernia may also be responsible for a chronic secondary anemia. This is probably due to intermittent oozing from erosions or even outright ulceration of a chronically congested herniated gastric pouch being constantly compressed by the muscular contractions of the diaphragm at the esophageal hiatus.

Most other symptoms usually ascribed to functional and organic disturbances of the upper gastrointestinal tract may also be present in hiatus hernia.

COMPLICATIONS

Hiatus hernia is a progressive condition. As the hernia gets larger in size, there results a disruption of the normal closing mechanism, especially in the sliding type of hernia, so that regurgitation of acid chyme into the lower esophagus takes place, with resultant inflammatory changes. If this is allowed to go unchecked, ulceration and subsequent scarring may set in, so that a stricture will form, with its obstructive symptoms.

At first a small hiatus hernia is easily reducible or may even be inconstant in its appearance and size. As the herniation gets larger it becomes more or less fixed. Its size and appearance, however, still vary with position and respiratory phase. It may be seen only in the prone and not in the upright position. Eventually it becomes fixed by adhesions. Then the pocket is irreducible or incarcerated. Strangulation or obstruction secondary to a volvulus, inflammatory edema, or adhesions may then take place. There may be traumatic erosions or ulcerations with massive hemorrhage. Persistent spasm with "curling" of the esophagus may occur at intervals. A carcinoma may also develop within the hiatal pocket.

In paraesophageal hiatus hernia complications are not as common, especially in the early stages. Compression by the herniated pocket alongside the esophagus actually prevents regurgitation. As the hernia gets larger it weakens the attachment of the lower esophagus, allowing

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for progressive sliding as well, so that a mixed-type hernia develops, and this is prone to all the complications mentioned above.

DIFFERENTIAL DIAGNOSIS

Surgical

Acquired sliding concentric or short-esophagus type of hiatus hernia has to be differentiated from a congenital short esophagus. At one time many of the acquired short-esophagus type of hernias were being called "congenital short esophagus." Now we know that the congenital type is quite rare. Roentgenologically the two are indistinguishable. The congenital type may be suggested in younger patients. A congenital short esophagus is not a hernia and on operation will show no sac, which is a feature of all acquired hernias. The sac cannot be seen roentgenographically, and surgery offers the only proof.

Roentgenologic

Hiatus hernia and its complications must be differentiated roentgenologically also from epiphrenic diverticula; chalasias, achalasia, and cardiospasm; stricture and carcinoma of the lower esophagus; esophageal varices; prolapse of gastric mucosa into the lower esophagus; and contractile rings of the lower esophagus.

Epiphrenic Diverticula. These are diagnosed by demonstrating a neck or direct continuity of the esophageal mucosa with the pouch. Chalasias, or persistently relaxed vestibule, is much more common in children and is due to cardioesophageal relaxation.⁴

Cardiospasm. Proper identification of the various component structures of the gastroesophageal segment of expulsion is essential to the diagnosis. In achalasia there is a persistent spasm of the vestibule with resultant dilatation of the esophagus above. Intermittent spasm with failure of the vestibule to relax, during relatively short periods, has been encountered. This may be the preliminary stage to the eventual development of cardiospasm. The latter is characterized by a beaklike contraction at the distal end of the esophagus, at the site of the inferior esophageal sphincter, with progressive dilatation and stasis of opaque media above this point. This area of narrowing has to be differentiated from esophagitis and carcinoma. In esophagitis there is marked irritability, and seldom is there obstruction except in the presence of a stricture.

Stricture and Carcinoma. A stricture is usually located above the level of the inferior esophageal sphincter. Carcinoma of the annular

type presents a rigid tubular contraction which is in most cases not perfectly smooth or symmetrical, obstruction is not as marked as in cardiospasm. However, the greatest dilation of the esophagus seen by us turned out to be not cardiospasm but a carcinoma.

Esophageal Varices. Cobbled or grooved irregularities and scalloped edges in a somewhat dilated esophagus indicate the presence of esophageal varices. The oil-contrast technic is particularly useful in demonstrating these varices.⁵ Films should be taken in the prone or Trendelenburg RAO position and in full expiration.

Prolapse of Gastric Mucosa. A mushroomlike inconstant filling defect at the lower end of the esophagus suggests prolapse of the gastric mucosa into the lower esophagus particularly during belching or regurgitation. It is due to a redundant gastric mucosa.⁶

Contractile Ring. Recently there has been reported⁷ a new entity, a contractile ring in the lower esophagus. This may be either a congenital band or hypertrophy of the inferior esophageal sphincter. It is noted on a full esophagus. There is no evident obstruction.

TREATMENT

Hiatus hernia is not a disease but a mechanical derangement. Thus, the cure can be only the surgical repair of the faulty mechanics. Medical prophylactic and symptomatic treatment has its value, however, especially when surgical repair cannot guarantee against recurrence. Therapeutic considerations involve the age, sex, and type of patient; his occupation; length of symptoms if any; the presence or absence of digestive symptoms; the cardiac status of the patient; the presence of complications; the type of hernia; and so on.

Medical Measures

If the patient is asymptomatic, precautionary measures should be taken, such as avoidance of tight abdominal binders or corsets, not going to bed immediately following a heavy meal, avoiding physical exercise involving squatting or heavy lifting. If the patient's occupation entails such strains, an attempt should be made to correct them.

Individual symptoms should be treated according to their manifestations. Carbonated drinks should be avoided, although alkalis and antispasmodics are given. A bland diet, frequent small feedings, and propping the patient up in bed at night are helpful. Surgery should be contemplated in all patients with a sliding or unusually large hernia, even in the absence of symptoms, if regurgitation can be demonstrated

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repeatedly roentgenologically. In the presence of symptoms every case has to be evaluated singly, especially in the presence of complications.

Surgical Approaches

When surgery is indicated there are two routes—transabdominal⁸ and transthoracic.⁹ Both have their advantages, but the latter is gaining in popularity. Here, again, every case should be individualized. If an exploratory laparotomy is desired at the same time or if there are pleural or thoracic complications, the abdominal route should be used. In most instances, the thoracic approach appears to offer a better repair with less frequent recurrences. The short-esophagus type of sliding hernia can be handled better with this technic because there is wider exposure of the operative field, and fewer postoperative complications result. The sac is not necessarily dissected out or even incised. However, reduction of the hernia and repair particularly of the posterior margins of the widened esophageal hiatus are most important. In addition, the lengthened phrenoesophageal membrane may be incised and sutured to the under-surface of the diaphragm. Or the greater curvature of the stomach may be fixed to the diaphragm to allow adhesions to form at the newly repaired esophageal hiatal site. Some surgeons repair the defect in the esophageal hiatus and move the esophagus forward to a new opening.¹⁰

The phrenic nerve is temporarily or permanently interrupted by some surgeons in the belief that this will allow for relaxation of the esophageal hiatus, thus permitting a better repair and healing. However, recent physiologic experimental studies in man carried out by artificial stimulation of the phrenic nerve do not corroborate the usefulness of this procedure. Relaxation of the esophageal hiatus after sectioning of the phrenic nerve could not be demonstrated.¹¹

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American Gastroscopic Society

The annual meeting of the American Gastroscopic Society will be held June 10 and 11, 1956, in Chicago, Illinois.

The Scientific Session will be held Sunday, June 10, at the Hotel Knickerbocker. A partial list of topics to be discussed includes anesthetics for gastroscopy, gastroscopic techniques, gastroscopic biopsy, and flexible-tube esophagoscopy. The business meeting and the Annual Banquet will be the closing events of the day.

The Clinical Session, to be held Monday, June 11, at Cook County Hospital will consist of demonstrations of esophagoscopy under general anesthesia, the esophagogastroscope, and two techniques of gastrobiopsy.

—Book Preview

We are privileged to present a series of excerpts from a forthcoming book, *Practical Diagnosis and Treatment of Liver Disease*, by Carroll M. Leevy, M.D. We wish to acknowledge our appreciation of the cooperation and help that Dr. Leevy has extended in the preparation of portions of his book for "Previews."—THE EDITORS.

Clinical Diagnosis of Liver Disease

I. Signs and Symptoms

LIVER disease should be suspected whenever there is a history of jaundice, dietary imbalance, alcoholism, exposure to hepatotoxins, or the presence of diseases which commonly cause hepatocellular injury. Fatty liver and nutritional cirrhosis are found in patients with improper diet, alcoholism, drug addiction, or systemic disease. Liver disease is frequent in patients with carbon tetrachloride, arsenic, phosphorus, beryllium, and other chemical intoxication, and is an integral part of many viral, bacterial, fungal, and parasitic infections. Hepatic abnormalities are demonstrable in most patients with heart failure, biliary obstruction, and metastatic neoplastic disease.

A thorough medical history is important in studies of liver disease. Viral hepatitis is suggested with the onset of malaise and icterus 6 weeks after receipt of plasma or other blood products. Nutritional cirrhosis is present in most chronic alcoholic patients with poor food habits who develop jaundice, ascites, and hematemesis. Hemobilia should be suspected when abdominal trauma is followed by recurrent jaundice, melena, pain in the right upper quadrant, and signs and symptoms of peripheral vascular collapse. Liver abscess is the most probable cause for cough, chills, fever, and right chest and scapular pain in the patient with amebic dysentery.

Suggestive signs of liver disease include changes in liver size or texture, tenderness or pain over the hepatic area; jaundice, spider angiomas, hepatic fetor, bleeding esophageal varices, splenomegaly, and ascites. Laboratory studies are often required to properly assess signs and symptoms.

Liver Size

An accurate estimate of liver size is important to preparation for aspiration liver biopsy and to establishment of a base line for subse-

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quent study. Physical examination is the best method for evaluating the size of the liver. The examiner should be seated and the patient recumbent, with head extended and legs drawn up. The surface area occupied by the liver is determined by percussion. The upper border is normally at the level of the fifth intercostal space in the midclavicular line, and the lower border extends to the edge of the right costal cage. Displacement, atrophy, or enlargement of the liver is determined by alterations in percussion findings.

The lower edge of the liver should be palpated whenever possible. Obesity, ascites, and muscular abdominal walls interfere with palpation. Palpation is facilitated by using the fingertips and making movements from the wrist. When the liver edge is below the thoracic cage, its extent should be recorded in centimeters. The right lobe is measured from the lowest costal cartilage in the midclavicular line. The left lobe is measured from the ensiform cartilage in the midsternal line, and from the thoracic cage in the left midclavicular line.

X-ray studies for liver size are helpful as a supplement to physical examination. The liver is best visualized if air is injected into the colon and the stomach distended with air.¹ Routine abdominal roentgenograms demonstrate liver enlargement; chest x-rays show an elevated right diaphragm with upward enlargement of the liver from an abscess or neoplastic infiltration (Fig. 1). Special radiologic techniques permit a reliable estimate of liver size. Gastrointestinal x-rays, cholecystography, cholangiography, or pyelography indirectly establish the presence of liver enlargement.

Hepatomegaly is the most frequently encountered clinical sign of liver disease. An increase in size is sometimes difficult to detect, as an enlarged liver may not be felt and a palpable liver may be of normal size. A liver which is palpable but not enlarged is displaced as a result of change in thoracic-abdominal relationships.

Liver enlargement is due to fatty changes, inflammation, bile stasis, congestion, fibrosis, regenerated liver cells, or infiltration by foreign materials. We have observed 30 cases of enlarged liver without detectable histologic abnormalities. Hepatomegaly regresses when reversible processes respond to treatment. Hepatomegaly persists when it is due to regenerated liver lobules or mature fibrous connective tissue.

The liver is frequently smaller than normal in the late phase of cirrhosis and in fulminant hepatitis. Rapid reduction in liver size is a grave prognostic sign and is accompanied by early death.¹ Atrophy is

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Fig. 1. Gastrointestinal x-ray, demonstrating elevation of the right diaphragm and distortion of the duodenum due to hepatic enlargement from amebic abscess of the liver.

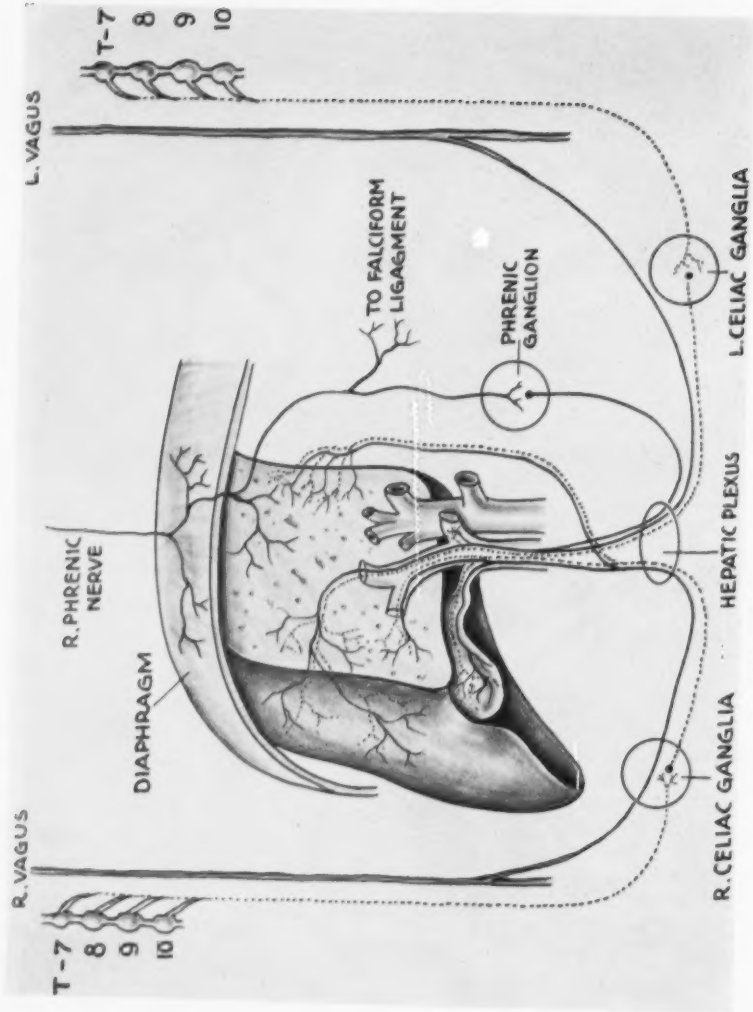


Fig. 2. Nerve supply of the liver.

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occasionally selective and may primarily involve but a single lobe of the liver.²

Liver Texture

Palpation of the liver permits the clinician to tell whether the surface of this organ is smooth or nodular, and to distinguish between a soft, firm, and hard liver. Nodularity is due to liver-cell regeneration, neoplastic disease, or other infiltrative processes. Clinical data sometimes permit a decision as to the cause of nodulation; however, biopsy is desirable for diagnosis.

The liver is normally soft but becomes firm or hard as a result of pathologic changes. Fatty infiltration, bile stasis, and passive congestion produce firm livers. Fibrosis, regeneration of liver cells, and bile-duct proliferation also cause hardening of the liver. In the end stages of cirrhosis, the liver has a rocklike consistency on palpation. The most marked degree of hardening of the liver occurs in patients with metastatic neoplastic infiltration or primary liver cancer.

Hepatic Tenderness and Pain

Tenderness of the liver is a common finding and often provides the first diagnostic clue in hepatic disease. Pain is usually mild; occasionally it is severe and simulates an acute condition in the abdomen requiring surgery. Liver pain results from stretching of the hepatic capsule, traction on the coronary and falciform ligaments, inflammation of the hepatic parenchyma, or perihepatitis.³ The afferent pathways for liver pain are in the hepatic and phrenic plexuses (Fig. 2).

Gradual increase in liver size does not cause pain, although it produces the sensation of abdominal heaviness. Rapid enlargement of the liver is accompanied by tenderness and occasionally severe pain. Diagnostic difficulty is encountered when tenderness or pain is not accompanied by liver enlargement, jaundice, or other clinical changes. Viral hepatitis without jaundice is notably confusing in this respect. Surgical exploration is often undertaken because of the degree and character of pain in patients with fatty liver, viral hepatitis, amebic abscess, metastatic carcinoma, and acute hepatic congestion.

Causes of Pain

Fatty liver has most frequently simulated conditions requiring surgery in our experience. Symptoms have been attributed to distention of the hepatic capsule and/or rupture of extracellular fatty cysts with resulting inflammation of the parenchyma. In alcoholism,

porphyruria, acute pancreatitis, and gastritis have been considered in the differential diagnosis. Viral hepatitis has been the second most common cause. Two patients with postnecrotic scarring and chronic active hepatitis had recurrent severe abdominal pain necessitating exploration. The mechanism responsible for abdominal pain is obscure in these instances, although it appears to be related to parenchymal inflammation. Rapid distention of the hepatic capsule and traction on hepatic ligaments appeared to produce symptoms of an acute abdomen in patients with liver abscess, metastatic carcinoma, and passive congestion.

Gonococcal perihepatitis complicating a salpingitis is associated with severe pain in the right upper quadrant of the abdomen which is referred to the shoulder region. Physical findings include fever, abdominal tenderness, muscular guarding, and ileus. Pelvic examination with cervical and urethral smears and cultures provides the diagnosis. At operation, there is a localized peritonitis with fibrin over the anterior surface of the liver.

Extravasation of blood or introduction of air beneath the hepatic capsule is responsible for the hepatic tenderness and pain seen after completing a needle biopsy of the liver. Pain is sometimes referred to the region of the liver in disease of the diaphragm, gallbladder, pleura, or heart. Patients with acute cholecystitis, diaphragmatic pleurisy, pleurodynia, pneumonia, or coronary insufficiency are suspected of having liver disease when there is localization of pain to the right upper quadrant of the abdomen.

Jaundice and Pruritus

Jaundice is often the presenting sign of liver disease. It reflects an increase in circulating bilirubin or bilirubin-globin. Blood serum is cleared of bilirubin as long as sufficient normal functioning hepatic tissue is present. Jaundice is detected by inspection when the serum bilirubin reaches 2.0 mg./100 cc. It is readily recognized by inspecting the sclera in daylight. This is the most reliable site in pigmented individuals.

Jaundice in hepatic disease is due to primary liver-cell dysfunction, biliary obstruction, and/or hemolysis. Liver-cell necrosis is the underlying cause for icterus in hepatitis, heart failure, and nutritional cirrhosis. Intrahepatic obstruction of small bile capillaries due to cholangiolar injury is also responsible for bilirubin accumulation. This mechanism is characteristic of viral and toxic hepatitis, but may occur

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in other types of liver disease. One fourth of patients with primary liver disease who develop jaundice have some evidence of biliary obstruction by laboratory tests. Histologic study may show inflammatory changes in the portal area or the connective-tissue stroma which encircles small bile ducts. Rarely, fat, amyloid, or neoplastic infiltration causes mechanical obstruction to bile outflow. In several instances in our clinic, marked jaundice has accompanied fatty liver, and subsequent events suggest that icterus was due to compression of small bile ducts by extracellular fat.

Case Report

CLINICAL FEATURES

M. H., a 54-year-old laborer, was hospitalized because of anorexia associated with weakness and jaundice. There was a history of eating poorly due to consumption of 1-2 pints of whiskey each day for several years. Physical examination revealed icterus and liver enlargement 6 cm. below the costal cage; there was no splenomegaly, spider angioma, hepatic fetor, collateral circulation, or fluid retention.

TABLE I
Biochemical and Histologic Findings in a Case of Simulated Extrahepatic Biliary Obstruction

	Before therapy	After 2 months of therapy
Biochemical study		
Serum bilirubin (mg./100 cc.)	34.0	0.1
Urine bile	4+	0
Urine urobilinogen	0	1:20
Bromsulfalein (%)	—	0
Serum alkaline		
Phosphatase (B.U.)	15.0	3.0
Total serum cholesterol (mg./100 cc.)	567.0	415.0
Cholesterol esters (mg./100 cc.)	85.0	274.0
Serum albumin (Gm./100 cc.)	2.3	2.8
Serum globulin (Gm./100 cc.)	3.3	3.9
Cephalin flocculation	2+	0
Thymol turbidity (units)	2.0	2.0
Glycogen storage rise in blood sugar (mg./100 cc.)	12.0	40.0
Histologic study		
Fibrosis	0	0
Fat	4+	0
Regeneration	1+	1+
Bile stasis	2+	0
Infiltration	2+	1+
Necrosis	0	0
Other	0	0
Pathologic diagnosis	Fatty liver with bile stasis	Normal liver

Diagnosis of extrahepatic biliary obstruction was made but surgical intervention was delayed because of pathologic findings on liver biopsy, which resulted in diagnosis of fatty liver with bile stasis. The patient was treated with bed rest, a diet of 350 Gm. of carbohydrate, 150 Gm. of protein, 100 Gm. of fat, 2 Gm. each of choline and methionine 3 times daily, and multivitamins. Clinical, biochemical, and histologic abnormalities disappeared on this regimen (Table 1). A gallbladder series performed after icterus had receded was normal.

COMMENT

This case demonstrates the ability of intracellular hepatic disease to produce mechanical obstruction to bile outflow and to simulate extrahepatic biliary obstruction.

Hemolysis causes jaundice in patients with liver disease who receive banked blood where a large number of the red cells are no longer viable. Less commonly hemolytic reactions are due to isohemolysins.

The degree of jaundice is not correlated with the severity of liver disease. Jaundice provides little index to prognosis, as many patients with a reversible lesion of the liver such as viral hepatitis or fatty liver have marked icterus. Jaundice is accompanied by pruritus when bile salts accumulate in the skin. Sometimes itching precedes clinical icterus and permits the clinician to anticipate elevation of the serum bilirubin. Pruritus is more common and of greater intensity in patients with jaundice due to biliary obstruction; however, this sign is not helpful in deciding etiology.

Differentiation of Etiologies

Jaundice due to hepatic disease must be differentiated from that caused by hemolytic disease and extrahepatic obstruction. Likewise, it must be distinguished from constitutional hyperbilirubinemia, or "familial non-hemolytic jaundice." These terms have been used to designate slight or latent jaundice found in a familial disease of unknown origin.⁴ In some instances, pigment is present in the liver cells of these individuals; in the usual case, however, needle biopsy shows no abnormalities. It has been suggested that pigmented liver cells comprise a distinct clinicopathologic entity,⁵ since most patients with this finding have abnormal liver-function tests, demonstrate no response to cholecystography, and exhibit an enlarged, tender liver at some time during the course of the disease. We have observed one patient with constitutional hyperbilirubinemia who had liver-cell

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pigmentation, good visualization of the gallbladder, and a lack of any physical evidence of liver disease. Recognition of this disease is important to prevent unnecessary surgical procedures. It usually occurs in young people, produces intermittent jaundice, and is aggravated by intercurrent disease.

The symptom complex and physical signs permit a correct decision as to the cause of jaundice in 75 per cent of patients. Biochemical liver-function tests and needle biopsy of the liver increase diagnostic accuracy to 95 per cent. Laboratory study is particularly important in patients with two mechanisms contributing to icterus.

Xanthomatosis and Skin Pigmentation

Xanthomas or lipid deposits in the skin occur with persistent hyperlipemia due to biliary obstruction. They are often seen in patients with chronic jaundice in both extrahepatic biliary obstruction and primary cholangiolar disease. Xanthomata plana are yellowish, slightly raised papules found most often over the flexor areas of joints and on the eyelids. Xanthomata tuberosa are larger and may grow to the size of a lemon. They are found over extensor surfaces. Xanthomas may decrease in size or disappear with relief of obstruction and reduction of hypercholesterolemia.

Increased skin pigmentation is noted in patients with prolonged jaundice, hemochromatosis, and certain neoplasms which involve the liver. Rarely nutritional liver disease causes darkening of the skin. Increased skin melanin or hemosiderin are responsible for color changes. Pigmentary change must be differentiated from that seen in adrenal insufficiency, drug intoxication, and other nonhepatic mechanisms.

Spider Angiomas

Spider angiomas, prominent skin capillaries, and telangiectasis are commonly observed in patients with liver disease, and provide a diagnostic clue in obscure cases. Spider angiomas are rare in carcinomatous metastases to the liver, the early phases of obstructive jaundice, and hepatic congestion in heart failure. They frequently diminish in size and disappear with subsidence of viral hepatitis, or improvement of hepatic function in patients with nutritional cirrhosis.

Spider angiomas are prominent around the face, neck, shoulders, and upper extremities. They consist of a centrally elevated, erythematous body 0.5–1.5 mm. in diameter from which radiate dilated, vascular branches to give the appearance of a spider. Pulsations are dis-

cernible under a magnifying glass or by palpation. Pressure interferes with their filling.

The cause of spider angiomas is unknown. There is some correlation of spider angiomas with the level of blood estrogens. This suggests that abnormal steroid metabolism may be responsible for their appearance.⁶ Histologically, they represent either a direct arteriovenous anastomosis or an overgrown end artery with branching arterioles and capillaries. In addition to being present in liver disease, spider angiomas also occur congenitally and are seen in pregnancy, rheumatic disease, and endocrine disorders.

Hepatic Fetor (Liver Breath)

A sweetish, musty odor resembling that observed in decayed fruit is often noted on the breath of patients with hepatic insufficiency. Occasionally, it is prominent enough to fill an entire room. The odor occurs predominantly in patients with severe hepatic fibrosis and is often present in fulminant viral hepatitis. It is usually noted when hepatic coma supervenes in the terminal phases of liver disease. Fetor is rarely present in patients with fatty liver, chronic passive congestion, or neoplastic infiltration of the liver. This odor is not specific and is seen in the absence of liver disease. We have noted it in patients with heart failure receiving thiomercaptans as diuretic agents. Concentrated urine from patients with fetor contains a material which has a similar smell and has chemical and physical properties of a tertiary amine.⁷ Methyl mercaptan has been isolated from the urine of a patient with fetor, and this, coupled with a high plasma level of methionine, has led to the suggestion that the mercaptan arises by hydrolytic or reductive fission of the sulphur-carbon bond in methionine.⁸

The presence and intensity of fetor hepaticus caused by liver disease indicates the gravity of the disease. Survival rates are inversely proportional to the intensity of the odor. Death often occurs within 3 to 6 months after this sign is noted. However, several patients with diffuse hepatic fibrosis have been followed for 5 years after detection of liver breath. Liver fetor disappears with improvement of general hepatic reserve.

Constitutional Symptoms

Both acute and chronic liver disease are accompanied by such non-specific symptoms as anorexia, weight loss, weakness, and malaise.

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These symptoms may be related to toxemia or reflect metabolic disturbances incident to hepatic dysfunction. Loss of appetite occurs predominantly in acutely ill patients with icterus, ascites, and sensorial changes. It is rarely due to an enlarged liver which mechanically compresses the stomach. Weight loss results from inadequate food intake, inability to assimilate foodstuffs, and negative nitrogen balance.

Weakness and malaise sometime constitute chief complaints in patients with both active and inactive hepatic disease. Muscular weakness has been attributed to disuse atrophy of bed rest and an abnormality in energy metabolism imposed by nutritional deficiency or interference with enzyme systems. This often presents a problem in differential diagnosis and will be discussed at another time.

(The next chapter will be on Circulatory Involvement, Fluid Imbalance, and Mental Changes.)

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EDITORIAL

Antispasmodics: From Empiricism to Controlled Experimentation

MANY YEARS HAVE PASSED since the belladonna alkaloids were first observed to inhibit certain motor and secretory functions of the intestinal tract. Dissatisfaction with the side effects attending the use of atropine has led to the development of hundreds of synthetic substitutes, each of which acts chiefly by competing with acetylcholine, at the postganglionic parasympathetic nerve ending, for the "receptor substance" of the effector cell in gland or muscle layer. Despite the profusion of these "antispasmodics," despite their wide clinical use, and despite many years of intensive pharmacologic study in experimental animals, certain important misconceptions prevail.

SIDE EFFECTS

The first misconception concerns their side effects. Atropine is highly potent and inexpensive; the chief justification for substitute compounds is the hope of inhibiting the intestine without producing dryness of the mouth or blurring of vision. Brief reflection on their mechanism of action suggests that this hope is unlikely to be fulfilled: the salivary glands and the ciliary muscles receive the same kind of cholinergic innervation as does the intestine. Yet for each new "antispasmodic" drug there are glowing reports of clinical efficacy without side effects. Scrutiny shows that the usual criterion of effectiveness is control of highly variable, subjective symptoms, and that the significance of placebo effects has been ignored. Further experience with each compound has cast doubt on its clinical effectiveness in recommended dosages. Surely, the time has come to insist upon the principle of the controlled experiment, preferably of the "double-blind" test procedure, which has clarified the role of vasodilators in angina pectoris,¹ of analgesics in postoperative pain,² and even of cortisone in ulcerative colitis.³

Dosage

The doses originally recommended for the compounds are educated guesses based on animal experimentation. The animal usually receives

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the drug parenterally, the human patient orally. The animal is quiet, even anesthetized; the patient is alert, often anxious. It is not surprising, therefore, that when direct observations are made^{4, 5, 6, 7} of the effects of "antispasmodics" on human intestinal motility and secretion, the effective human dose proves to be much larger than expected. The dose which objectively inhibits the intestine usually also dries the mouth and blurs vision. It is gratifying to note that the doses of many new compounds are being chosen only after direct objective study in human subjects. In the light of the many studies of this kind, it seems unlikely that pharmacologically useful action on the intestine will be obtained with this type of drug without the minor discomforts of atropine, although several of the newer compounds exceed atropine in the degree of intestinal inhibition afforded by well-tolerated doses.^{5, 6}

Uses of Side Effects

If side effects are here to stay, we can nevertheless make good use of them. In the treatment of acute rheumatic fever, adequate dosage of salicylates has long been measured by the production of tinnitus. Patients with gout are advised to take colchicine until diarrhea is produced. Similarly, patients requiring "antispasmodics" can be told that a dry mouth is their assurance of adequate dosage. Those who are unwilling to accept such discomfort can be given lower dosage for placebo effect, but the physician should not delude himself concerning the nature of this treatment.

ANTICHOLINERGICS

The second important misconception involves the words *antispasmodic* and *anticholinergic*. These are not synonymous. *Antispasmodic* activity is a clinical desideratum, improperly attributed to atropine and related compounds. The term suggests the replacement of excessive and uncoordinated movements with tranquil, rhythmic motility. What is achieved by these drugs is rather the quantitative reduction of *all* motility and secretion, without alteration of its basic pattern. This is due to the site of action of these drugs—at the post-ganglionic cholinergic nerve ending rather than at the integrating centers in the brain. Such *anticholinergic* activity is useful in an uncomplicated duodenal ulcer, where it inhibits the hyperfunctioning stomach and produces, in effect, a "medical vagotomy." In a patient with an obstructed ulcer, however, it depresses the peristaltic activity of the

stomach more than the stronger contractions of the spastic pylorus and proximal duodenum, with the result of worsening obstruction. In patients with irritable colon, anticholinergic activity is valuable in controlling diarrhea, which seems to be related to simple excess of cholinergic stimulation,⁸ but is a hindrance to those with constipation, where propulsive activity of the proximal colon appears to be inhibited more strongly than spasm of the sigmoid.

TRUE ANTISPASMODIC ACTION

The search for a true antispasmodic, one which will not merely weaken motility but alter its disordered pattern, still lies before us. It seems likely that such a compound must have central action, on synapses probably in the medulla or the hypothalamus. The pharmacologic actions of compounds such as chlorpromazine and reserpine are being scrutinized with special interest. Pressing forward in this direction may not only meet a long-recognized clinical need, but also provide us with important basic knowledge of the mechanisms underlying disordered function of the intestine.

THOMAS P. ALMY, M.D.

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